

Application No. 09/761,686  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

**AMENDMENTS TO THE CLAIMS:**

This listing of claims will replace all prior versions and listings of claims in the application:

**Listing of Claims:**

1. (currently amended) A monomeric monocyclic peptide which interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3, wherein the monomeric monocyclic peptide comprises a cyclic core consisting of a core sequence and a first linking group at one end of the core sequence, and a second linking group at the other end of the core sequence, wherein the:

(1) — a core sequence ~~which~~ consists of

(a) a receptor-binding loop 1, 2 or 3 of VEGF-D, selected from the group consisting of SEQ ID NO:7; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13 and SEQ ID NO:14,

(b) a ~~corresponding~~ loop fragment consisting of a sequence selected from the group consisting of SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13 and SEQ ID NO:14 with one or more conservative amino acid substitutions, or

Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

(c) a ~~corresponding~~ loop fragment consisting of a sequence selected from the group consisting of SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13 and SEQ ID NO:14 with one or two amino acid residues deleted or inserted,

~~(2) a first linking group at one end of the core sequence, and~~

~~(3) a second linking group at the other end of the core sequence,~~

wherein the first and second linking groups are connected to form a constraint that cyclizes the peptide such that receptor-binding loops 1, 2 or 3 or the corresponding loop fragment mimics a native conformation in the corresponding region of VEGF, VEGF-C or VEGF-D.

2. (Previously Presented) The monomeric monocyclic peptide according to claim 1, which interferes with a biological activity of VEGF-C or VEGF-D mediated by VEGF receptor-2.

3. (Previously Presented) The monomeric monocyclic peptide according to claim 1, which interferes with a biological activity of VEGF-C or VEGF-D mediated by VEGF receptor-3.

4. (withdrawn) A dimeric bicyclic peptide comprising two monomeric monocyclic peptides according to claim 1, linked together.

5-11. (cancelled)

Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

12. (Previously Presented) A monomeric, monocyclic peptide produced by a method comprising:

obtaining a receptor-binding loop 1, 2 and 3 of VEGF-D,

modifying the loop with one or more conservative amino acid substitutions to produce a modified loop;

measuring beta-beta carbon separation distances on opposing antiparallel strands of the modified loop;

selecting a modified loop with a beta-beta carbon location with a separation distance of less than 6 angstroms;

providing a linking group in each opposing antiparallel strand at the selected beta-beta carbon location, and

cyclizing the peptide by linking the linking groups to form a constraint that cyclizes the peptide such that receptor-binding loops 1, 2 or 3 or the corresponding loop fragment mimics a respective native conformation, wherein a monomeric, monocyclic peptide, which interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

13. (cancelled)

Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

14. (withdrawn) A dimeric bicyclic peptide comprising two monomeric monocyclic peptides according to claim 12, linked together.
15. (withdrawn) A dimeric bicyclic peptide according to claim 14, wherein the two monomeric monocyclic peptides are identical.
16. (withdrawn) A dimeric bicyclic peptide according to claim 14, wherein the two monomeric monocyclic peptides are different.
17. (withdrawn) A dimeric bicyclic peptide according to claim 14, which interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.
18. (Previously Presented) The cyclic peptide according to claim 12, wherein the method further comprises deleting at least one amino acid residue from said loop fragment prior to cyclizing the peptide, wherein the cyclic peptide interferes with a biological activity of at least one factor selected from the group consisting of VEGF, VEGF-C, and VEGF-D mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.
- 19-22. (cancelled)
23. (Previously Presented) A composition of matter comprising a monomeric monocyclic peptide according to claim 1, and at least one pharmaceutical carrier or adjuvant.

Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

24. (original) A composition of matter comprising a monomeric monocyclic peptide according to claim 12, and at least one pharmaceutical carrier or adjuvant.

25. (withdrawn) A composition of matter comprising a dimeric, bicyclic peptide according to claim 14, and at least one pharmaceutical carrier or adjuvant.

26. (original) A composition of matter comprising a cyclic peptide according to claim 18, and at least one pharmaceutical carrier or adjuvant.

27-48. (cancelled)

49. (Currently Amended) A cyclic peptide comprising a peptide sequence selected from the group consisting of ~~SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:10; SEQ ID NO:11; SEQ ID NO:12; SEQ ID NO:13 and SEQ ID NO:14.~~

50. (Previously Presented) The cyclic peptide according to claim 49, wherein said peptide is a monomeric monocyclic peptide.

51. (Previously Presented) The cyclic peptide according to claim 50, wherein said peptide interferes with a biological activity mediated by at least one receptor selected from the group consisting of VEGF receptor-2 and VEGF receptor-3.

Application No. 09/761,686  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

52. (Currently Amended) The cyclic peptide according to claim 1 49, ~~comprising~~ consisting of SEQ ID NO:5.
53. (Currently Amended) The cyclic peptide according to claim 1 49, ~~comprising~~ consisting of SEQ ID NO:6.
54. (Previously Presented) The cyclic peptide according to claim 49, comprising SEQ ID NO:7.
55. (Previously Presented) The cyclic peptide according to claim 49, comprising SEQ ID NO:13.
56. (withdrawn) A cyclic peptide according to claim 49, wherein said peptide is a dimeric bicyclic peptide comprising two monocyclic peptides linked together.
57. (withdrawn) A cyclic peptide according to claim 56, wherein said two monocyclic peptides are identical.
58. (withdrawn) A cyclic peptide according to claim 56, wherein said two monocyclic peptides are different.
59. (withdrawn) A cyclic peptide according to claim 56 comprising SEQ ID NO:8 or SEQ ID NO:9.
60. (withdrawn) A cyclic peptide according to claim 59, wherein said peptide is a homodimer comprising two monocyclic peptides of SEQ ID NO:8 linked together.

Application No. 09/761,638  
Reply to Office Action of October 14, 2004

Attorney Docket No.:48505US

61. (withdrawn) A cyclic peptide according to claim 59, wherein said peptide is a homodimer comprising two monocyclic peptides of SEQ ID NO:9 linked together.

62. (withdrawn) A cyclic peptide according to claim 59, wherein said peptide is a heterodimer comprising a monocyclic peptide of SEQ ID NO:8 linked to monocyclic peptide of SEQ ID NO:9.

63. (Previously Presented) The cyclic peptide according to claim 12, which interferes with the activity of VEGF-D and/or VEGF-C, but not VEGF, mediated by VEGF receptor-2.

64-71. (cancelled)

72. (previously presented) The monomeric monocyclic peptide of claim 1, wherein the constraint maintains a beta-beta carbon separation distance between opposing anti-parallel strands of the loop or loop fragment at less than 6 angstrom.

73. (previously presented) The monomeric monocyclic peptide of claim 1, wherein the first or second linking group comprises 1 to 20 carbon atoms, or 1 to 10 heteroatoms, which may be straight chain or branched which contain one or more saturated, unsaturated or aromatic ring.

74. (previously presented) The monomeric monocyclic peptide of claim 73, wherein the hetero atom is selected from the group consisting of N, O, S, and P.

Application No. 09/761,686  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

75. (previously presented) The monomeric monocyclic peptide of claim 1, wherein the constraint is an amide, ester, disulfide, thioether, ether, phosphate, or amine group.

76. (previously presented) The monomeric monocyclic peptide of claim 75, wherein the constraint is formed between an N-terminal amine and a C-terminal carboxyl of the peptide.

77. (previously presented) The monomeric monocyclic peptide of claim 76, wherein the constraint is formed directly via an amide bond between an N-terminal nitrogen and a C-terminal carbonyl.

78. (previously presented) The monomeric monocyclic peptide of claim 76, wherein the constraint is formed indirectly via a spacer group.

79. (previously presented) The monomeric monocyclic peptide of claim 78, wherein the spacer group is 4-amino carboxylic acid.

80. (previously presented) The monomeric monocyclic peptide of claim 75, wherein the constraint is a covalent bond between side chains of two amino acid residues of the peptide.

81. (previously presented) The monomeric monocyclic peptide of claim 1, wherein the constraint is an amide bond between a lysine residue and an aspartic acid or glutamic acid residue, a disulfide bond between two cysteine residues, or a thioether bond between a cysteine residue and a 4-halogenated amino acid residue.



Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

82. (previously presented) The monomeric monocyclic peptide of claim 81, wherein the constraint is a disulfide bond formed between two cysteine residues.

83. (previously presented) The monomeric monocyclic peptide of claim 80, wherein residues contributing the side chains may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

84. (previously presented) The monomeric monocyclic peptide of claim 75, wherein the constraint is an amide bond between a side chain of an amino acid and the C-terminal carboxyl or N-terminal amine.

85. (previously presented) The monomeric monocyclic peptide of claim 84, wherein residue contributing the side chain may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

86. (previously presented) The monomeric monocyclic peptide of Claim 1, wherein the core sequence consists of 4 to 11 amino acid residues.

87. (previously presented) The monomeric monocyclic peptide of Claim 86, wherein the core sequence consists of 6 to 11 amino acid residues.

88. (previously presented) A monomeric, monocyclic peptide according to Claim 12, wherein the linking group is a cysteine residue, and the

Application No. 09/761,686  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

peptide is cyclized by oxidizing the cysteine residues to form a disulfide bridge between strands.

89. (withdrawn) A dimeric bicyclic peptide comprising two monomeric monocyclic peptide according to Claim 1.

90. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint maintains a beta-beta carbon separation distance between opposing anti-parallel strands of the loop or loop fragment at less than 6 angstrom.

91. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the first or second linking group comprises 1 to 20 carbon atoms, or 1 to 10 heteroatoms, which may be straight chain or branched which contain one or more saturated, unsaturated or aromatic ring.

92. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the hetero atom is selected from the group consisting of N, O, S, and P.

93. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is an amide, ester, disulfide, thioether, ether, phosphate, or amine group.

94. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is formed between an N-terminal amine and a C-terminal carboxyl acid function of the peptide.

Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

95. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is formed directly via an amide bond between an N-terminal nitrogen and a C-terminal carbonyl.

96. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is formed indirectly via a spacer group.

97. (withdrawn) The dimeric bicyclic peptide of claim 96, wherein the spacer group is 4-amino carboxylic acid.

98. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is a covalent bond between side chains of two amino acid residues of the peptide.

99. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is an amide bond between a lysine residue and an aspartic acid or glutamic acid residue, a disulfide bond between two cysteine residues, or a thioether bond between a cysteine residue and a 4-halogenated amino acid residue.

100. (withdrawn) The dimeric bicyclic peptide of claim 99, wherein the constraint is a disulfide bond formed between two cystein residues.

101. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein residues contributing the side chains may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.

Application No. 09/761,636  
Reply to Office Action of October 14, 2004

Attorney Docket No.: 48505US

102. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein the constraint is an amide bond between a side chain of an amino acid and the C-terminal carboxyl or N-terminal amine.

103. (withdrawn) The dimeric bicyclic peptide of claim 89, wherein residue contributing the side chain may be derived from the loop sequence itself, or may be incorporated into or added on to the loop sequence.